510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
DEVICE AND INSTRUMENT TEMPLATE

A. 510(k) Number:
k041002

B. Purpose for Submission:
New device

C. Analyte:
Anti-gliadin IgA and IgG antibodies
Anti-tissue transglutaminase (anti-tTG) IgA antibodies

D. Type of Test:
Homogeneous fluorescent-based microparticles immunoassay using flow cytometry readings

E. Applicant:
Biomedical Diagnostics (BMD)

F. Proprietary and Established Names:
FIDIS™ Celiac on the FIDIS™ Analyser

G. Regulatory Information:

1. Regulation section:
   21 CFR 866.5660 Multiple Autoantibodies Immunological Test System
   21 CFR 866.5750 Radioallergosorbent (RAST) Immunological Test System
2. Classification:
   Class II
3. Product Code:
   MVM Autoantibodies, Endomysial (tissue transglutaminase)
   MST Antibodies, Gliadin
4. Panel:
   Immunology 82

H. Intended Use:

1. Intended use(s):
   The FIDIS™ Celiac kit is a fluorescent immunoassay for the semi-quantitative simultaneous detection of antibodies directed against Gliadin and Tissue Transglutaminase Enzyme. Celiac IgA is designed for the simultaneous detection of human IgA isotype antibodies directed against Gliadin and Tissue Transglutaminase Enzyme. Celiac IgG is designed for the detection of human IgG isotype antibodies directed against Gliadin. The

presence of these antibodies can be used in conjunction with clinical findings to aid in the diagnosis of Celiac disease. For in vitro diagnostic use.

2. Indication(s) for use:
   The FIDIS™ Celiac kit is a semi-quantitative homogeneous fluorescent-based microparticles immunoassay using flow cytometry readings. Celiac IgA is designed for the simultaneous detection of human IgA isotype antibodies directed against Gliadin and Tissue Transglutaminase Enzyme. Celiac IgG is designed for the detection of human IgG isotype antibodies directed against Gliadin. The presence of these antibodies can be used in conjunction with clinical findings to aid in the diagnosis of Celiac disease. The FIDIS™ Celiac kit is to be used on serum only and used on the FIDIS™ Analyser, software and washer.

3. Special condition for use statement(s):
   Prescription use

4. Special instrument Requirements:
   FIDIS™ Analyser (Luminex 100 IS plus FIDIS™ MLX Software)

I. Device Description:

The device consists of the following:

- One vial of Celiac IgA microsphere suspension. The suspension contains a mixture of color-coded microspheres sensitized by either one of the 2 antigens, gliadin or human recombinant tissue transglutaminase (tTG)
- One vial of Celiac IgG microsphere suspension. The suspension contains a set of color-coded microspheres sensitized by the antigen gliadin.
- Calibrator IgA: The calibrator is titrated for IgA antibodies against gliadin and tTG.
- Calibrator IgG: The calibrator is titrated for IgG antibodies against gliadin.
- Positive controls: human sera containing IgA and IgG antibodies
- Negative control
- Goat anti-human IgA and anti-human IgG conjugate coupled to phycoerythrin
- PBS-Tween 10x concentrate
- Two 96 well microplate including a 1.2 µm filtering membrane and an opaque lid

J. Substantial Equivalence Information:

1. Predicate device name(s):
   BINDAZYME ELISA Human Anti-Gliadin IgG Kit
   BINDAZYME ELISA Human Anti-Gliadin IgA Kit
   BINDAZYME ELISA Human Anti-Tissue Transglutaminase [IgA] Kit

2. Predicate K number(s):
   K981929 (Anti-Gliadin IgG and IgA)
   K993612 (Anti-Tissue Transglutaminase IgA)

3. Comparison with predicate:

Similarities		
Item	**Device**	**Predicate**
Intended Use	Determination of IgA and IgG antibodies against gliadin and of IgA antibodies against tTG as an aid in the diagnosis of celiac disease	Same
Antigens	Gliadin (wheat gluten) and human recombinant tissue transglutaminase	Same
Wash step	Yes	Yes
Differences		
Item	**Device**	**Predicate**
Assay method	Fluorescent-based micro-particles immunoassay using flow cytometry	ELISA
Solid phase	Color-coded microspheres	Microtiter plate
Conjugate	Phycoerythrin	Horseradish peroxidase
Substrate	None	TMB
Detection method	Fluorescence	Colorimetry
Reading	Flow cytometer	Spectrophotometer

K. Standard/Guidance Document Referenced (if applicable):

"Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests; Draft Guidance for Industry and FDA Reviewers"; and "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices"

L. Test Principle:

FIDIS™ Celiac is based on the use of distinct uniform size color coded microspheres and a bench-top flow cytometer interfaced to a digital signal processing hardware and software. A red diode laser beam of the flow cytometer classifies each set of microspheres on the basis of its unique fluorescence intensity (red to orange), which allows identifying the analyte being tested. At the same time, a green laser beam illuminates the external second fluorescence molecule to quantify the specific reaction related to each analyte.

Each antigen required for the assay is covalently coupled to an individual set of microspheres through its surface functional groups. The different antigen coupled microspheres are mixed together to constitute the final microspheres reagent. Celiac IgA allows the detection of anti-gliadin and anti-tTG IgA isotype antibodies. Celiac IgG allows the detection of anti-gliadin IgG isotype antibodies.

The test is performed in a 96 well blank microplate including a filtering membrane at the bottom of the wells. In the first step, the sample is distributed in duplicate for the 2 isotypes selected in each well containing either the Celiac IgA microspheres mixture or the Celiac IgG microspheres mixture. If the samples tested contain one or more of the suspected antibodies, the antibody(ies) will bind to the corresponding antigen(s) on the microspheres. After incubation a wash step through a filtration process will eliminate the unbound antibodies.

A specific conjugate consisting of either goat anti-human IgA or IgG antibodies coupled to phycoerythrin is added to the mixture. It will bind to the previously captured antibodies. The reaction is then directly measured by the flow cytometer which categorizes each microspheres set according to its fluorescence color while simultaneously measuring the average fluorescence emitted by the conjugate. A calibration system allows the expression of titer in arbitrary units AU/mL or GU/mL by interpolation of the curve for antigenic specificity.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
   a. Precision/Reproducibility:
   To evaluate both the intra-assay and inter-assay reproducibility, patient sera samples were selected to include low (weakly positive), moderate and high positives for each analyte.

	Within-run (10 tests in the same run)		**Between-run (5 tests in 5 different runs)**	
Antibody specificity:	Mean value U/mL	CV (%)	Mean value U/mL	CV (%)
tTG IgA	41	3.9	42	3.7
tTG IgA	151	4.6	152	5.3
tTG IgA	318	4.0	323	7.0
Glia IgA	41	3.4	42	2.8
Glia IgA	71	2.3	72	2.4
Glia IgA	474	5.5	493	3.1
Glia IgG	69	2.3	70	5.6
Glia IgG	99	4.4	101	7.2
Glia IgG	151	3.5	155	4.6

   b. Linearity/assay reportable range:
   Linearity is sera dependent in the FIDIS™ assay system. The average binding capacity is the best compromise to represent the mean affinity and avidity of the antibody being studied. This capacity varies between samples and even within the same sample. The main variables characterizing these antibodies are the nature of the target epitopes and the quantity of antibodies recognizing each of these epitopes. The result of this measurement is strongly influenced

by the reaction conditions. The FIDIS™ Celiac assay has been set to express the average binding capacity at the current dilution (1:200) by a flow cytometric reading resulting from the median fluorescence value obtained from 400 microspheres per parameter. Further dilutions potentially give rise to inaccurate results because the reaction conditions and the equilibrium of the immunological reaction will be modified. The instrument was able to report results for samples up to 894 U/mL.

c. *Traceability (controls, calibrators, or method):*
None given.

d. *Detection limit:*
None given

e. *Analytical specificity:*
Sixty-one samples were selected for their potential biological interference (cryoglobulinemia, hypergammaglobulinemia, IgG and IgM monoclonal immunoglobulins, complement, rheumatoid factor, hemolyzed sera, lipemic sera and plasma). There were 10 positive results across the 61 samples tested.

	Gliadin IgG	Gliadin IgA	tTG IgA
	Number positive	Number positive	Number positive
Complement disorder n=15		1	
Cryoglobulinemia n=8	1	1	
RF positive n=8		4	
Hemolyzed n=6		1	
Hypergammaglobulinemia n=7			
IgG monoclonal immunoglobulin n=5			
IgM monoclonal immunoglobulin n=5			
Plasma n=4		1	1
Lipemia n=3			

f. *Assay cut-off:*
One hundred sixteen non-Celiac disease samples including 55 normal blood donor samples and 61 samples with potential biological interference (see analytical specificity) were run to establish the cut-offs for the assays. Results <15 U/mL are negative, 15-20 U/mL are considered borderline and results >20 U/mL are positive. Using the cut-off of <15 U/mL, 97.4 (113/116) were

negative for Gliadin IgG, 91.4% (106/116) were negative for Gliadin IgA, and 99.1% (115/116) were negative for tTG IgA.

2. Comparison studies:
   a. *Method comparison with predicate device:*
   The method comparisons with the predicate devices were performed on 182 samples: 66 samples related to celiac disease (suspected of having celiac disease), 55 samples from blood donors, and 61 samples selected for their potential biological interferences (see analytical specificity). Borderline results were considered negative for purposes of the calculations.

Gliadin IgA		Bindazyme	
		+	-
FIDIS	+	55	2
	-	16	109

Positive percent agreement: 55/71 = 77.5%
Negative percent agreement: 109/111 = 98.2%
Overall agreement: 164/182 = 90.1%

tTG IgA		Bindazyme	
		+	-
FIDIS	+	44	0
		3	135

Positive percent agreement: 44/47 = 93.6%
Negative percent agreement: 135/135 = 100%
Overall agreement: 179/182 = 98.3%

Gliadin IgG		Bindazyme	
		+	-
FIDIS	+	54	0
	-	6	122

Positive percent agreement: 54/60 = 90.0%
Negative percent agreement: 122/122 = 100%
Overall agreement: 176/182 = 96.7%

   b. *Matrix comparison:*
   Both assay use serum as matrix.

3. Clinical studies:
   a. *Clinical sensitivity:*
   Not given
   b. *Clinical specificity:*

Non-celiac			
n = 116	+	-	Clin. Specificity
Gliadin IgG	3	113	97.4%
Gliadin IgA	10	106	91.4%
tTG IgA	1	115	99.1%

c. Other clinical supportive data (when a and b are not applicable):
Not applicable

4. Clinical cut-off:
   Not furnished

5. Expected values/Reference range:
   The expected value in the normal population is negative. Four samples out of 55 (7%) tested positive tested positive for at least one antibody.

N. Instrument Name:
FIDIS™ Analyser (Luminex 100 IS plus FIDIS™ MLX software)

O. System Descriptions:

1. Modes of Operation:
   The operator manually pipets patient samples, calibrator, controls and reagents into a microtiter plate. Following incubation and washing, the reaction is read by flow cytometry and the fluorescent signal is converted to arbitrary units for reporting.
2. Software:
   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:
   Yes.
3. Sample Identification:
   Not applicable. The operator manually enters sample identification into the instrument for all wells.
4. Specimen Sampling and Handling:
   The operator manually pipettes reagents and samples into the microtiter plate and then manually loads the plate onto the instrument.
5. Assay Types:
   Homogeneous fluorescent-based microparticles immunoassay using flow cytometry
6. Reaction Types:
   Antigen/antibody binding detected and measured by flow cytometry
7. Calibration:
   There is a single level calibrator for each isotype included with the kit. The operator is instructed to include the calibrators with every run.

8. Quality Control:
   The operator is instructed to run both positive controls (containing IgA gliadin and tTG antibodies or IgG gliadin antibodies) and the negative controls with every run.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "L. Performance Characteristics" Section Of The SE Determination Decision Summary:

None

Q. Conclusion:

The submitted material in this premarket notification is complete and supports a substantial equivalence decision.